HED DOC. NO. 013576

**DATE:** June 22, 1999

**MEMORANDUM**

**SUBJECT:** ***PROPARGITE*** - Report of the Hazard Identification Assessment Review Committee.

**FROM:** Suhair Shallal, Toxicologist.
Reregistration Branch 4
Health Effects Division (7509C)

**THROUGH:** Pauline Wagner, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Jess Rowland, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

**TO:** Thurston Morton, Risk Assessor
Reregistration Branch 4
Health Effects Division (7509C)

**PC Code: 097601**

On June 3, 1999, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **PROPARGITE,** established a Reference Dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. HIARC re-assessed the Reference Dose (RfD) established in 1994, as well as the toxicological endpoints selected for acute dietary and occupational/residential exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to propargite as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

| | |
|---|---|
| Members present were: | Dave Anderson<br>Karen Hamernik<br>Pam Hurley<br>Mike Ioannou<br>Tina Levine<br>Nancy McCarroll<br>Nicole Paquette<br>Kathleen Raffaele<br>Jess Rowland<br>P.V. Shah<br>Pauline Wagner |
| Member(s) in absentia: | William Burnam<br>Virginia Dobozy<br>Sue Makris |

Data was presented by Suhair Shallal of the Reregistration Branch 4.

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| Also in attendance were: | Sanjivani Diwan/ RRB4<br>Ray Kent/ RRB4<br>Thurston Morton/ RRB4<br>Brenda Tarplee/ SAB<br>Abdullah Khasawinah/ RRB4 |

Data Presentation:
and
Report Presentation _____
Suhair Shallal,
Toxicologist

Report Concurrence: _____
Brenda Tarplee
Executive Secretary

cc: RD
Casewell file

## I. INTRODUCTION

On June 3, 1999, the Health Effects Division (HED) Hazard Identification Assessment Review Committee evaluated the toxicology data base of **PROPARGITE,** established a Reference Dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. HIARC re-assessed the Reference Dose (RfD) established in 1994, as well as the toxicological endpoints selected for acute dietary and occupational/residential exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to ethyl parathion as required by the Food Quality Protection Act (FQPA) of 1996.

## II. HAZARD IDENTIFICATION

### A. Acute Reference Dose (RfD)

Females 13-50 yrs.

Study Selected: Developmental Toxicity Study in Rabbits **§** 83-3

MRID No.: 41336301

Executive Summary:

In a developmental toxicity study (MRID 41336301), Omite (85% a.i.) was administered in corn oil by gavage to New Zealand White rabbits, 25 female per dose, at levels of 0, 2, 4, 6, 8, or 10 mg/kg/day) on gestation days (GD) 7-19.

One animal died in each of the 6 and 8 mg/kg/day dose group. However since no deaths occured at the HDT, these findings were considered incidental. A total of 8 abortions occured among all dose groups (3 at 4 mg/kg/day, 1 at 8 mg/kg/day, and 4 at 10 mg/kg/day). These rates are comparable to those found for historical controls and were therefore considered not to be treatment-related. These animals also displayed clinical signs including, hair loss, anogenital staining, decreased defecation and emaciated appearance. A reduction in body weight gain occurred at doses of 8 and 10 mg/kg/day during GD 7-20 (gain of 9 g and loss of 20 g, respectively, versus a gain of 114, 165 and 119 g for control, 2 and 4 mg/kg/day, respectively).

There were no treatment-related effects on the number of viable fetuses, implantation loss, mean fetal body weight, sex distribution, or mean uterine weight. Several malformations were found in the higher dose groups (8-10 mg/kg/day) including, fused sternebrae, fused skull bones, gallbladder agenesis, interrupted ossification of ribs, and short tail. Only the incidence of fused sternebrae at 10 mg/kg/day was considered to be significantly greater than that observed in study and historical controls.

**The maternal LOAEL is 8 mg/kg/day, based on decreased body weight gain. The maternal NOAEL is 6 mg/kg/day.**
**The developmental LOAEL is 10 mg/kg/day, based on increased incidence of fused sternebrae. The developmental NOAEL is 8 mg/kg/day.**

Dose and Endpoint for Establishing RfD:

8 mg/kg/day (developmental NOAEL) based on the increased incidence of fused sternebrae at the LOAEL of 10 mg/kg/day.

Uncertainty Factor (UF): 100 (10X interspecies, 10X intraspecies)

$$\textbf{Acute RfD (females 13-50)} = \frac{8 \text{ mg/kg}}{100 \text{ (UF)}} = \textbf{0.08 mg/kg}$$

Comments about Study/Endpoint/Uncertainty Factor:
The only studies available to predict possible risk to females of child-bearing age and fetuses are developmental and reproductive toxicity studies. Although developmental studies are conducted using repeat doses, in the developmental toxicity study in rats (MRID 41336301), we cannot discount the possibility that the developmental effect of fused sternebrae may have occurred after a single dose. The HIARC concluded that the NOAEL of 8 mg/kg/day with an uncertainty factor of 100 (10X interspecies, 10X intraspecies) would be appropriate for this subgroup of the population. In a previous TES committee meeting (12/1/93) no endpoint was established due to the lack of evidence to support an acute dietary exposure risk assessment.

**This Risk Assessment is required.**

**Acute Reference Dose (RfD)** -general population

Comments about Study/Endpoint/Uncertainty Factor:
No relevant effects following a single exposure were found in the available oral toxicity studies, including the developmental toxicity studies. Propargite is a catagory III chemical for oral toxicity. Even at very high doses, a relatively mild effect as noted in the following study.

In an oral range-finding study conducted on monkeys, Omite (93.3% a.i.) was administered to 5 female cynomolgus monkeys (1 animal/dose) by gavage in corn oil (5 ml/kg) at dose levels of 18, 105, 500, 1000 and 5000 mg/kg. After dosing, the animals were observed for 7 days and then sacrificed.

No mortality was reported at any dose level; however, animals did have soft feces at dose levels >18 mg/kg. Animal in the 5000 mg/kg dose group had a reduction in body weight at day 4, but by day 8 the animals had recovered. No treatment-related other clinical observations were noted; although, alkaline phosphatase levels did appear to be elevated. No compound-related lesions were evident.

**This risk assessment is not required.**

**B. Chronic Reference Dose (RfD)**

Study Selected: Chronic Oral and Carcinogenecity in Rats § 83-5

MRID No.:41750901

Executive Summary:

In a chronic toxicity/carcinogenicity study (MRID 41750901), Omite (87.2%, a.i.) was administered to 50 Sprague-Dawley Crl:CD BR rats/sex/dose (an additional 10 rats/sex/dose were sacrifice at 53 weeks) in 0.5% corn oil in the diet at dose levels of 0, 50, 80, 400 and 800 ppm (0, 2.38, 3.83, 19.24 and 38.87 mg/kg/day for males and 0, 2.95, 4.68, 23.58 and 49.36 mg/kg/day for females) for 24 months. These doses were selected as a result of a previously conducted 90-day study and an earlier chronic feeding study dated 1966.

Mortality for males (8/50 and 20/50 at 400 and 800 ppm, respectively)and for females (7/50 at 800 ppm) appears to be related to the increased incidence of undifferentiated sarcoma in the GI tract. Males displayed the greatest reduction in body weight gain at the 400 and 800 ppm dose levels during the initial weeks of the study (at 400 ppm, weeks 0-6: -9%, weeks 6-13: -8.7%, then recovered by week 28; at 800 ppm, weeks 0-6: -30%, weeks 6-13: -21.4%, weeks 13-28: -9%, then recovered by week 52). Females also experienced comparable body weight gain reduction at the 400 ppm dose level; however, at 800 ppm, females showed a stronger and more sustained adverse weight gain reduction than males (week 0-6: -26.3%, week 6-13: -24.9%, week 13-28: -41.1%, week 28-52: -30.3%). Food consumption showed comparable decreases for the 400 and 800 ppm dose groups (see attached table). No hematological changes that could be definitively attributed to the test material were noted. Total serum protein, calcium, globulin were reduced compared to controls and lead to an increase in the albumin/globulin ratio (see attached table). Relative weights of brain, liver and kidney were all found to be elevated in the 800 ppm dose level (see attached table). These changes were not associated with any histopathologic changes and may be related to body weight changes.

There were dose related increases in incidence of jejunum tumors in both sexes. The incidence values were 0, 0, 0, 10 and 15 tumors (0,0,0,17% and 25%)in males and 0, 1, 0, 1, and 9 tumors (0,2%,0,2% and 15%) in females for the control, 50, 80, 400, and 800 ppm dose groups, respectively (60 animals per group). The first indication of masses in the jejunum was at week 65. They were, however, not always associated with any increase in ulceration or other signs of irritation of the stomach or jejunum at terrmination.

Undifferentiated sarcoma of the GI tract is a rare tumor in rats. Historical control data reveal that only 1 male of 472 (in ten studies from 1984-1988) had tumors in the duodenum and none in the jejunum. No females had this type of tumor of 479(duodenum) and 465 (jejunum) animals examined. Tumors of the jejunum were seen in males and females receiving the highest doses of 400 and 800 ppm. The dosing was adequate to assess the carcinogenic potential of propargite.

**The LOAEL is 400 ppm (19.24 mg/kg/day) for males** due to increased mortality, decreased body weight and body weight gain, as well as, decreases in total protein and calcium. **The NOAEL is 80 ppm (3.83 mg/kg/day) for males.**

**The LOAEL is 800 ppm (49.36 mg/kg/day) for females** due to decreases in body weight and body weight gain. **The NOAEL is 400 ppm (23.58 mg/kg/day) for females.**

Dose/Endpoint for establishing the RfD Risk Assessment:
4 mg/kg/day based on decreased body weight and body weight gain and increased mortality at the LOAEL of 20 mg/kg/day.

Uncertainty Factor (UF): 100 (10X interspecies, 10X intraspecies)

$$\textbf{Chronic RfD} = \frac{4 \text{ mg/kg}}{100 \text{ (UF)}} = \textbf{0.04 mg/kg}$$

Comments about Study/Endpoint/Uncertainty Factor:
The selected endpoint is the NOAEL for males in the chronic toxicity and carcinogenicity study in rats and is supported by the reproduction study (MRID 41352401, see section 3 on page 7 of this document for executive summary) with the parental systemic NOAEL of 4 mg/kg/day. This endpoint is based on decreased body weight and body weight gain, as well as, changes in blood parameters at 20 mg/kg/day.

**This risk assessment is required.**

### C. Occupational/Residential Exposure

There are no registered residential uses at the present time; therefore, the end points selected are applicable only to occupational exposure risk assessments. **HIARC recognizes that the primary effect of PROPARGITE is severe skin irritation.** Propargite is considered corrosive and has been placed in Category I for both eye and dermal irritation in rabbits. There have also been documented reports of dermal and eye irritation developing in workers exposed to Propargite in the field. Evidence for its dermal sensitization potential have been noted; a study that provides conclusive results has not been possible due to the irritating properties of this chemical. Challenge doses in such study are usually conducted using the highest nonirritating dose; in the case of Propargite, these doses are extremely low and may not elicit a response.

#### 1. Dermal Absorption

In a dermal absorption study (MRID 40982503), Omite (89.87 % a.i.) was applied to lightly shaved backs (10 $cm^2$) of 5 groups of 4 Sprague-Dawley rats at dose levels of 0.05, 0.5 and 5 mg/kg/day for 0, 2, 4, 8 and 24 hours. Sacrifices occured immediately after washing at 0, 2 or 4 hours; for the 8 and 24 hour exposures, the skin was washed but sacrifices occured at 120 hours after administration of test material. A transient but significant increase in dermal absorption (wash in effect) was observed directly after the 8 and 24 hour washes at all doses tested. This effect may be due to the irritant properties of this chemical. No detectable radioactivity was observed in the blood samples from the 0.05 and 0.5 mg/kg 8 and 24 hour washed animals. At 5.0 mg/kg a few blood samples (8,24 and/or 48 hours) showed concentrations of test material of about 0.04 to 0.08 nmol/g. At the low dose of 0.05 mg/kg, there is no significant difference in the total percent absorbed with the 8 or 24 hour exposure (14.5% and 14.3% excreted, respectively).

At 0.5 and 5.0 mg/kg, the 24 hour exposure shows a significantly greater total absorption, 12.9% and 11.4% excreted compared to 8.8 % and 7.5% excreted for 8 hours, respectively.

In a second dermal absorption study (MRID 40982504), Omite (89.87 % a.i.) was applied to lightly shaved backs (10 $cm^2$) of 20 male Sprague-Dawley rats at dose levels of 0.05 mg/kg for 0, 2, 4, 8 and 24 hours. Sacrifices occurred immediately after washing at 0, 2 or 4 hours. For the 8 and 24 hour exposure groups, the skin was washed but sacrifices occurred at 120 hours after administration of test material. Dermal absorption of propargite for OMITE 6E formulation was <0.1% for exposures of 2 and 4 hours. Exposures of 8 and 24hours washed and carried to 120 hours showed absorptions of 4.3 and 8.2%, respectively. A transient but significant increase in dermal absorption (wash in effect) was observed directly after the 8 and 24 hour washes. This effect may be due to the irritant properties of this chemical. No detectable radioactivity was observed in the blood samples collected at 8, 24, 48, 72 and 96 hours from the 0.05 mg/kg animals washed 8 or 24 post exposure. The low total recovery for exposures of 4, 8 and 24 hours was attributed to one animal in each test group; however, when the data from those animals was not included recovery calculations are greatly improved.

Dermal Absorption Factor:

A 14% dermal absorption factor was selected based on the highest absorption/elimination noted in either of the studies cited above. This percentage is deemed valid since it corresponds to the amount of Propargite which was actually detected in the excretions of animals.

**2. Short-Term Dermal (1-7 days)**

Study Selected: Developmental Toxicity in Rabbits § 83-3

MRID No.: 41336301

Executive Summary: see Section A- Acute Reference Dose

Dose and Endpoint for Risk Assessment:

6 mg/kg/day (maternal NOAEL) based on reduction in body weight gain at the LOAEL of 8 mg/kg/day.

Comments about Study/Endpoint:.

A repeat dose dermal toxicity study (MRID 41284101) was available for consideration. In this study, Omite (85 % a.i.) was applied undiluted to the shaved backs of 5 New Zealand White rabbits/sex/dose at dose levels of 0, 0.1, 1.0, 10.0, and 100 mg/kg/day) for 6 hours. A total of fifteen applications were made, five days per week for three weeks. Signs of dermal irritation were seen at all dose levels. Lesions noted consisted of erythema, edema, atonia, desquamation, fissuring, eschar, exfoliation, blanching, coriaceousness. Histological examination revealed acanthosis, hyperkeratosis, inflammation, necrosis and abscess. **The LOAEL for dermal toxicity is 0.1 mg/kg/day, based on signs of dermal reaction. The NOAEL for dermal toxicity is <0.1 mg/kg/day. The LOAEL for systemic toxicity is >100 mg/kg/day, in the**

**absence of definite signs of systemic toxicity. The increased appearance of segmented neutrophils was probably related to the inflammation resulting from irritation at the site of application of the test material. In the absence of definite signs of toxicity, the systemic NOAEL is 100 mg/kg/day.**
The developmental toxicity study in rabbits was selected due to the absence of comparable systemic effects of reduced body weight gain in the 21-day repeat dermal toxicity study. Also, the maternal NOAEL of 8 mg/kg/day will be protective of the fetal effects which were seen at 10 mg/kg/day. Since an oral value was selected, a 14% dermal absorption factor should be used for risk assessment. A margin of exposure (MOE) of 100 is also added.

**This risk assessment is required.**

### 3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 2-generation reproduction in rats § 83-4

MRID No.: 41352401

Executive Summary:
In a two-generation reproduction study (MRID 41352401), Omite (87.2 % a.i.) was administered to 25 Crl:CDBR rats/sex/dose in their diet at dose levels of 0, 80, 400, and 800 ppm (0, 4, 20, and 40 mg/kg/day) for 10 weeks then mated to produce the $F_1$a generation. They were mated a second time after a 2 week rest period to produce the $F_1$b generation. The $F_1$b generation were treated in a similar manner to produce the $F_2$a and $F_2$b generation.

No compound related clinical signs or reactions were observed for either parental group. A decrease in body weight gain occurred for animals in the high dose and mid dose groups but recovered. Both food consumption and food efficiency were reduced at 400 and 800 ppm.

Necropsy revealed no compound related effects on gross or microscopic histological findings. There were no compound related adverse effects on the reproductive performance of any group. At the high dose, there were decreases in mean pup weight at birth and during the period of lactation.

**The systemic LOAEL is 400 ppm (20 mg/kg/day), based on decreased parental body weight, and food consumption. The systemic NOAEL is 80 ppm (4 mg/kg/day).**
**The developmental LOAEL is 800 ppm (40 mg/kg/day), based on reduction of pup weight during lactation. The developmental NOAEL is 400 ppm (20 mg/kg/day).**
**The reproductive LOAEL and NOAEL are > 800 ppm (40 mg/kg/day).**

Dose/Endpoint for Risk Assessment:
4 mg/kg/day (paternal systemic NOAEL) based reduction in parental body weight and food consumption at the LOAEL of 20 mg/kg/day.

Comments about Study/Endpoint:

The duration of exposure in this study was found to be more appropriate for the intermediate-term exposure period of concern (7 days to several months). Since an oral value was selected, a 14% dermal absorption factor is also to be integrated in the risk assessment.

**This risk assessment is required.**

**4. Long-Term Dermal (Several Months to Life-Time)**

Study Selected: Chronic Feeding and Carcinogenicity in Rats § 83-5

MRID No.: 41750901

Executive Summary: See Chronic RfD section

Dose and Endpoint for Risk Assessment:
4 mg/kg/day based on increased mortality and decreased body weight and body weight gain at the LOAEL of 20 mg/kg/day.

Comments about Study/Endpoint:.
This dose/endpoint/study was also selected for the chronic dietary risk assessment due to the appropriateness of the duration of exposure. A 14% dermal absorption factor will also be integrated for risk assessment purposes.

**This risk assessment is required.**

**5. Inhalation Exposure (Any Time period)**

Study Selected: Acute Inhalation § 81-3

MRID No.: 42857003

Executive Summary:
In an acute inhalation toxicity study (MRID 42857003), CD Crl:CD BR rats (5/sex/dose) were exposed by inhalation route (nose only) to Omite (85%, a.i.) by heating in a three necked flask at concentrations of 0.31, 0.80, and 1.3 mg/L for 4 hours.

**$LC_{50}$ males = 0.95 mg/L**
**females = 0.95 mg/L for**
**combined = 0.89 mg/L**

Mortality at the lowest level was observed within 24 hours of exposure (1/10). At the 0.80 mg/L dose, deaths occurred on day 2 and 3 (2/10). At the 0.31 mg/L dose, animals recovered and were

sacrificed at day 15, the animals at 0.80 mg/L were observed an additional week and showed incomplete recovery. At 1.3 mg/L, all animals (10/10) died between days 2 and 17. Signs of toxicity included labored respiration, decreased activity, nasal discharge, anogenital staining, matted coats, at all levels. The animals at 0.80 and 1.3 mg/L showed moist rales, grasping, perioral encrustation as well. Weight loss was observed in all animals; however, the survivors exceeded their pretest weights at termination. Necropsy revealed discoloration of the lungs. Some showed signs of gastrointestinal distress and discoloration of the skin.

Dose/Endpoint for Risk Assessment:

0.31 mg/L or 49.6 mg/kg (LOAEL) mortality occurred at this endpoint (1/10).

[conversion mg/L to mg/kg:
0.31 mg/L X 10 L/hr X 4 hrs = 12.4 mg; 12.4 mg / 0.25 kg = 49.6 mg/kg]

Comments about Study/Endpoint:

Although this is an acute LC50 study, it was selected for risk assessment since mortality was seen at all dose levels, including the lowest dose. Survivors exhibited clinical signs (weight loss and histopathology to the lungs). An additional uncertainty factor of 10X was selected due to the use of a LOAEL and the concern for the severity of the effects (death) at the lowest dose (0.31 mg/L or 49.6 mg/kg).

**This risk assessment is required.**

### D. Recommendation for Aggregate Exposure Risk Assessments

**HIARC recognizes that PROPARGITE causes severe skin irritation. There are no registered residential uses at the present time. Therefore, aggregate exposure risk assessment will be limited to food and water.**

### E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

**The MOE of 100 is adequate for dermal occupational exposure at all time durations. A MOE of 1000 is required for inhalation exposure for all exposure durations due to the severity of the effect (death) at the lowest dose (0.31 mg/L or 49.6 mg/kg) tested in an acute inhalation toxicity study.**

## III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

### A. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 41750901

Executive Summary

In a chronic toxicity/carcinogenicity study (MRID 41750901), Omite (87.2%, a.i.) was administered to 50 Sprague-Dawley Crl:CD BR rats/sex/dose (an additional 10 rats/sex/dose were sacrifice at 53 weeks) in 0.5% corn oil in the diet at dose levels of 0, 50, 80, 400 and 800 ppm (0, 2.38, 3.83, 19.24 and 38.87 mg/kg/day for males and 0, 2.95, 4.68, 23.58 and 49.36 mg/kg/day for females) for 24 months. These doses were selected as a result of a previously conducted 90-day study and an earlier chronic feeding study dated 1966.

Mortality for males (8/50 and 20/50 at 400 and 800 ppm, respectively)and for females (7/50 at 800 ppm) appears to be related to the increased incidence of undifferentiated sarcoma in the GI tract. Males displayed the greatest reduction in body weight at the 400 and 800 ppm dose levels during the initial weeks of the study (at 400 ppm, weeks 0-6: -9%, weeks 6-13: -8.7%, then recovered by week 28; at 800 ppm, weeks 0-6: -30%, weeks 6-13: -21.4%, weeks 13-28: -9%, then recovered by week 52). Females also experienced comparable body weight gain reduction at the 400 ppm dose level; however, at 800 ppm, females showed a stronger and more sustained adverse weight gain reduction than males (week 0-6: -26.3%, week 6-13: -24.9%, week 13-28: -41.1%, week 28-52: -30.3%) . Food consumption showed comparable decreases for the 400 and 800 ppm dose groups. No hematological changes that could be definitively attributed to the test material were noted. Total serum protein, calcium, globulin were reduced compared to controls and lead to an increase in the albumin/globulin ratio. Relative weights of brain, liver and kidney were all found to be elevated in the 800 ppm dose level. These changes were not associated with any histopathologic changes and may be related to body weight changes.

There were dose related increases in incidence of jejunum tumors in both sexes. The incidence values were 0, 0, 0, 10 and 15 tumors (0,0,0,17% and 25%)in males and 0, 1, 0, 1, and 9 tumors (0,2%,0,2% and 15%) in females for the control, 50, 80, 400, and 800 ppm dose groups, respectively (60 animals per group). The first indication of masses in the jejunum was at week 65. They were, however, not always associated with any increase in ulceration or other signs of irritation of the stomach or jejunum.

Undifferentiated sarcoma of the GI tract is a rare tumor in rats. Historical control data reveal that only 1 male of 472 (in ten studies from 1984-1988) had tumors in the duodenum and none in the jejunum. No females had this type of tumor of 479 (duodenum) and 465 (jejunum) animals examined.

Tumors of the jejunum were seen in males and females receiving the highest doses of 400 and 800 ppm. The dosing was adequate to assess the carcinogenic potential of propargite.

**The LOAEL is 400 ppm (19.24 mg/kg/day) for males** due to increased mortality, decreased body weight and body weight gain, as well as, decreases in total protein and calcium. **The NOAEL is 80 ppm (3.83 mg/kg/day) for males.**

**The LOAEL is 800 ppm (38.87 mg/kg/day) for females** due to decreases in body weight and body weight gain. **The NOAEL is 400 ppm (23.58 mg/kg/day) for females.**

Adequacy of the Dose Levels Tested

The dose level were adequate to evaluate to carcinogenic potential of propargite

**A Second Confirmatory Study:**

MRID No. 42837201

Executive Summary

In a carcinogenecity study (MRID 42837201), Omite (89.87 % a.i.) was administered to 2 groups of 60 male Charles River CD rats in epoxidized soybean oil at dose levels of 0 or 800 ppm (0 or 36.3 mg/kg/day) for 2 year. For interim sacrifice, 10 rats/dose were sacrificed at one year.

There was decreased survival after week 78 and no clinical behavioral effects were noted. Food consumption decreased (15-20%) along with body weight gain. Treated rats weighed at 13 weeks, 44 weeks, as well as at study termination were found to have a lower body weight (17.5%, 17.4% and 15.7%, respectively) than controls. Changes in absolute and relative weights of liver, kidney, brain and testes were considered to be due to decreased body weight since they were not accompanied by histopathological findings. Therefore, these changes were not considered toxicologically significant. No tumors were found during the interim sacrifice. The incidence of undifferentiated sarcoma in the jejunum was found to increase significantly with treatment, 0/50 for controls versus 23/47 (49%) for the 800 ppm dose group. These tumors were found to contribute to mortality at the high dose. There was no evidence of non-neoplastic lesions such as ulcerations in the jejunum or duodenum that may have contributed to the initiation of the tumors.

Discussion of Tumor Data

Undifferentiated sarcoma of the GI tract is a rare tumor in rats. The nearly 50% increase in the incidence of this tumor at the 800 ppm dose in the second confirmatory study is therefore of toxicologic significance. Historical control data reveal that only 1 male of 472 (in ten studies from 1984-1988) had tumors in the duodenum and none in the jejunum. No females had this type of tumor of 479 (duodenum) and 465 (jejunum) animals examined.

Tumors of the jejunum were seen in males and females receiving the highest doses of 400 and 800 ppm in the first study. The incidence appeared to be dose related, especially in males.

Adequacy of the Dose Levels Tested

The dose level were adequate to evaluate to carcinogenic potential of propargite

**2. Carcinogenicity Study in Mice**

MRID No. 00130942

Executive Summary

In an carcinogenecity study (MRID 00130942), Omite (purity not provided) was administered to 5 groups of 60 CD-1 mice/sex in corn oil in the diet at dose levels of 0, 50, 160, 500 and 1000 ppm (0, 7, 23, 71 and 143 mg/kg/day) for 18 months. A satellite group of 15 mice/sex was dosed with either 0, 500 or 1000 ppm (0, 71 or 143 mg/kg/day) for 12 months. These doses were selected as a result of a range-finding study.

No compound related mortality, effects on hematologic parameters, reduction in food consumption or body weight gain were noted.
Adrenal gland and uterine absolute and relative weights were found to increase (relative weights increased 33% and 46% for adrenals and uterus, respectively). These effects were not accompanied by histopathological changes and therefore, were not considered toxicologically significant. Tumors of the gastrointestinal tract were noted in all dose groups including controls. However, none of the tumors resembled undifferentiated sarcoma seen in the rat study and no dose response was evident. In conclusion, no evidence of carcinogenicity or systemic toxicity was seen at dose levels up to 1000 ppm (143 mg/kg/day). The dosing was inadequate to access the carcinogenic potential of propargite.

**The LOAEL for systemic toxicity is >1000 ppm (143 mg/kg/day).**

This carcinogenicity study in the mouse is Unacceptable/Guideline and does not satisfy the guideline requirement as it was conducted prior to the establishment of FIFRA guidelines. The purity of the test material was not reported and the highest dose (1000 ppm) tested was not adequate to access its carcinogenic potential.

Discussion of Tumor Data

In the mouse study, no evidence of carcinogenicity could be found. This may be due the inadequacy of the dose levels. There was no systemic toxicity associated with any of the doses, including the highest dose tested, 1000 ppm (143 mg/kg).

Adequacy of the Dose Levels Tested

The dosing was **inadequate** to access the carcinogenic potential of propargite. The study could have been conducted at higher dose levels. The RfD committee (1992) recommended that no new mouse carcinogenicity study was needed since the rat was shown to be more sensitive.

**C. Classification of Carcinogenic Potential**

Propargite is classified as a B2 carcinogen. An ad hoc committee will be scheduled to discuss revising the nomenclature of classification as well as to consider the relevance of cell proliferation studies submitted by the registrant to establishing a mode of action.

## IV. MUTAGENICITY

Several mutagenicity studies have been submitted. All studies indicate that propargite is NOT a mutagen. The following table summaries the mutagenicity database.

**Mutagenicity Profile for Propargite (097601)**

| Guideline # | TYPE OF STUDY SUBMITTED | MRID No(s) YEAR | Comments (NOAEL/LOAEL) | Classification |
|---|---|---|---|---|
| 84-2 | Mutagenicity / Gene Mutation | 42885001/ 1993 | No evidence of mutagenecity was observed at any dose level in either the presence or absence of metabolic activation. In contrast, positive controls treated with ethylmethane sulfonate (EMS) gave definitive positive results. | Acceptable/ Guideline |
| 84-2 | CHO/HGPRT mut assay (Acetone) | 42815201/ 1993 | No evidence of mutagenecity was observed at any dose level in either the presence or absence of metabolic activation. In contrast, positive controls treated with ethylmethane sulfonate (EMS) gave definitive positive results. | Acceptable/ Guideline |
| 84-2 | CHO/HGPRT mut assay (DMSO) Micronucleus cytogenetic Assay-mouse | 43502202/ 1994 | Two males were found dead on day 3 and one female died on day 1. Clinical signs included lethargy and diarrhea in mice treated with 75 and 150 mg/kg. In these dose groups, there was a decrease in erythropoesis but no increase in micronucleated PCEs was noted. Propargite was considered negative in this mouse micronucleus assay. | Acceptable/ Guideline |
| 84-2 | Mutagenicity / Structural Chromosomal Aberr-MNT | 40384603/ 1987 | Propargite was found to be negative for inducing micronuclei in bone marrow polychromatic erythrocytes of mice treated with single i.p. doses at levels up to cytotoxicity (150 mg/kg). | Acceptable/ Guideline |
| 84-2 | Mutagenicity / DNA damage/repair | 40384602/ 1987 | Omite was found to be very cytotoxic at levels above 1.67 µg/ml. However it was negative for inducing unscheduled DNA "repair" synthesis (UDS) in rat hepatocyte cultures exposed to levels below 1.67 µg/ml. The positive control, 2-aminoacetofluorene, induced a significant increase in net nuclear grains. | Acceptable/ Guideline |

## V. FQPA CONSIDERATIONS

### A. Neurotoxicity

No neurotoxicity was observed in any of the studies submitted for Propargite. Acute and developmental neurotoxicity studies have not been submitted for this chemical and are not required.

### B. Developmental Toxicity

See Section II- A. Acute RfD for the executive summary of the rabbit developmental study (MRID 41336301).

A rat developmental study (MRID 41346501) is also available:

Executive Summary:
In a developmental toxicity study (MRID 41346501), Omite (85% a.i.) was administered in corn oil by gavage to Sprague-Dawley rats, 45 female per dose, at levels of 0, 6, 12, 18, 25, or 105 mg/kg/day) on gestation days (GD) 6-15 of gestation.

No treatment-related maternal deaths occurred in this study. Animals in the 105 mg/kg/day dose group were found to display anogenital staining(21 incidences) and body surface staining (7 incidences). A significant reduction in body weight gain for the high dose group during GD 6-9 of the study was considered treatment-related. No fetal effects were noted for animals sacrificed at day 20 of gestation. No treatment related external, visceral, or skeletal malformations or variations were found upon examination of the fetuses.

**The maternal LOAEL is 105 mg/kg/day, based on decreased body weight, anogenital staining, and body surface staining. The maternal NOAEL is 25 mg/kg/day.**
**The developmental NOAEL is 105 mg/kg/day (Highest Dose Tested).**

### C. Reproductive Toxicity

See Section II- C3 Intermediate-term dermal for the executive summary of a 2-generation reproductive study (MRID 41352401) in rats.

### D. Additional information from the literature (IF AVAILABLE)

In the literature, citations refer to incidences of dermal irritation and conjunctivitis among workers in the field.

### E. Determination of Susceptibility

No increased susceptibility is seen for infants and children. In rabbit and rat developmental toxicity studies, the effects seen in fetuses are at dose levels equal to or greater than doses where maternal toxicity is seen. In a 2-generation reproductive toxicity study in rats, the effects seen in fetuses were found at dose levels equal to or greater than doses where maternal effects occur.

### F. Recommendation for a Developmental Neurotoxicity Study

**The HIARC** determined that a developmental neurotoxicity study is not required since:

- No neurotoxic effects are seen in any of the submitted studies.
- No neurotoxicity concerns seen in the open literature.
- No abnormalities to the fetal nervous system were seen in the developmental and reproductive toxicity studies.

### G. Hazard-Based Recommendation of the FQPA Safety Factor

Based on hazard alone, the HIARC recommends the removal of the additional 10X FQPA safety factor due to: 1) the completeness of the toxicology database and 2) the lack of increased susceptibility following *in utero* exposure to rats and rabbits and pre/post natal exposure to rats.

## VI. HAZARD CHARACTERIZATION

Propargite is considered **corrosive** and has been placed in Category I **for both eye and dermal irritation** in rabbits. There have also been documented reports of dermal and eye irritation developing in workers exposed to Propargite in the field. Evidence for its dermal sensitization potential have been noted; a study that provides conclusive results has not been possible due to the irritating properties of this chemical. However, there is low acute toxicity (Category III) via the oral (rat: $LD_{50}$ = 2639 mg/kg for males, 2947 mg/kg for females) and dermal (rabbit: $LD_{50}$ > 2000 mg/kg) routes of exposure. The available studies demonstrate no increased sensitivity of rats or rabbits to in utero and/or postnatal exposure to Propargite. In both rat and rabbit developmental studies (MRID 41346501 and 41336301, respectively), maternal toxicity was shown to occur at a lower dose level than for fetuses [for rat, the maternal NOAEL is 25 mg/kg/day and the developmental NOAEL is 105 mg/kg/day (Highest Dose Tested); for rabbit the maternal NOAEL is 6 mg/kg/day and the developmental NOAEL is 8 mg/kg/day]. The multi-generation reproduction study (MRID 41352401) also reveals very low toxicity with parental/offspring NOAEL's (4/20 mg/kg) based upon body weight loss only.

A battery of mutagenicity studies adequately demonstrates the lack of mutagenic effects exerted by this chemical. There is, however, a carcinogenicity concern associated with Propargite and it has been classified as a B2 carcinogen (CARC July 23, 1992) based upon the development of tumors in the jejunum of Sprague-Dawley rats at 400 and 800 ppm dose levels (no carcinogenicity in CD-1 mouse or Wistar rats). In a memo submitted on February 16, 1995 by Bernice Fisher, Biostatistician, a revised $Q_1^*$ of 1.71 X $10^{-1}$ $(mg/kg/day)^{-1}$ was established (a $Q_1^*$ of 3.1 X $10^{-2}$ $(mg/kg/day)^{-1}$ was cited in the February 8, 1994 TES report). Cell proliferation studies (MRID 43766801) have been conducted in an effort to establish a mode of action for the carcinogenicity. The most prevalent clinical signs associated with this chemical are weight loss and GI (stomach and jejunum) perturbations.

Six metabolites have been identified, one of which appears only in female rat urine (the list of metabolites and their structures are attached). The major routes of excretion are the urinary, fecal, and biliary routes. Metabolite 1 (1-[4-(2,x-dihydroxycyclohexoxy) phenyl]-2,2-dimethyl acetic acid) is the most prevalent metabolite in the urine of male rats, while Metabolite 3 (1-[4-(1,1-dimethyl-2-hydroxyethyl)phenoxyl]-2,4,5-cyclohexanetriol) is the most prevalent in the urine of female rats. Metabolite 6 is only found in female urine (1-[4-(2,4,5-trihydroxycyclohexoxy) phenyl]-2,2-dimethyl acetic acid). The kidney and liver are the organs which retained the most metabolite at a rate of $\leq$1.5 % of the administered dose in rat, rabbit and monkey. There were no

qualitative differences found in the formation of metabolites in mouse versus rat. Pharmacokinetic studies revealed that propargite is absorbed thru the GI tract 5-7 times faster in mice than rat . Mice also eliminated the material twice as fast as rats.

## VII. DATA GAPS

No acceptable subchronic oral toxicity studies are available; however, chronic study are sufficient for the establishment of a chronic RfD. The requirement of a 90-inhalation study was waived ( Doc. No. 007221) on September 21, 1988.

## VIII. ACUTE TOXICITY

**Acute Toxicity of PROPARGITE**

| Guideline No. | Study Type | MRID #(S). | Results | Toxicity Category |
|---|---|---|---|---|
| 81-1 | Acute Oral-Rat | 42857001 | $LD_{50}$ = 2639 mg/kg for males<br>2947 mg/kg for females<br>2800 mg/kg combined | III |
| 81-2 | Acute Dermal-Rabbit | 42857002 | $LD_{50}$ > 2000 mg/kg | III |
| 81-3 | Acute Inhalation-Rat | 42857003 | $LC_{50}$ = 0.95 mg/L for males<br>0.95 mg/L for females<br>0.89 mg/L combined | III |
| 81-4 | Primary Eye Irritation-Rabbit | 42857004 | Corrosive | I |
| 81-5 | Primary Skin Irritation-Rabbit | 42857005 | Corrosive | I |
| 81-6 | Dermal Sensitization-Guinea Pig | 42857006 | Sensitizer | N/A |

## IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

| EXPOSURE SCENARIO | DOSE (mg/kg/day) | ENDPOINT | STUDY TYPE/ MRID |
|---|---|---|---|
| Acute Dietary-females 13-50 | NOAEL= 8<br><br>UF = 100 | Increased incidence of fused sternebrae. | Developmental Toxicity in Rabbits 41336301 |

| | | | |
|---|---|---|---|
| Acute Dietary-general population | NOAEL= N/A<br><br>UF = N/A | No relevant single exposure endpoint was identified. | N/A |
| | **Acute RfD (females 13-50) = 0.08 mg/kg/day Acute RfD (Gen. Pop.) = N/A** | | |
| Chronic Dietary | NOAEL = 4<br><br>UF = 100 | Decreased body weight / body weight gain and increased mortality. | Chronic Feeding and Carcinogenicity in Rats 41750901 |
| | | **Chronic RfD = 0.04 mg/kg/day** | |
| Short-Term [1] (Dermal) | NOAEL= 6 | maternal systemic LOAEL based on decreased body weight | Developmental Toxicity in Rabbits 41336301 |
| Intermediate-Term [1] (Dermal) | NOAEL= 4 | parental LOAEL based on reduction in body weight | Reproductive Toxicity in Rats 41352401 |
| Long-Term [1] (Dermal) | NOAEL= 4 | Decreased body weight / body weight gain and increased mortality. | Chronic Feeding and Carcinogenicity in Rats 41750901 |
| Short Term [2] (Inhalation) | LOAEL= 0.31mg/L or 49.6 mg/kg | LOAEL of 0.31 based on increased mortality | Acute Inhalation 42857003 |
| Intermediate Term [2] (Inhalation) | | | |
| Long Term [2] (Inhalation) | | | |

[1] A 14% dermal absorption factor will be used for risk assessment and an MOE of 100.
[2] An MOE of 1000 was selected, including a 10X factor due to the severity of the effects at the lowest dose tested.